Rodent Analgesia

Amy L. Miller, PhD[a,b], Claire A. Richardson, BVM&S, MRCVS[a,b,*]

KEYWORDS

- Rodent • Analgesia • Mice • Rats • Guinea pigs • Chinchillas

Rodents of all species are frequently kept as companion animals, with increasing client expectations for the care of their animals. Fortunately, specialist veterinary interest and information is now available for treatment of rodents. In the field of rodent analgesia particularly, much can be learned from the methods developed for preventing and alleviating pain in animals undergoing research studies in laboratories throughout the world. This article reviews advances in pain detection techniques in rodents and makes recommendations on analgesic agents that are available for the alleviation of pain.

RECOGNIZING PAIN

To effectively alleviate pain in animals we must first be able to recognize it. Recognition of pain and its intensity allows assessment of employed analgesic regimens to ensure that the treatments are both effective and appropriate. As animals cannot report the intensity of their pain, alternative methods of pain assessment must be used. Although this remains a challenge in veterinary practice, an awareness of ongoing research in pain assessment in animals can help us to detect and alleviate pain in pet rodents.

Objective Indicators of Pain in Animals

Objective methods of assessing pain are essential to ensure appropriate pain relief is provided. These methods often include monitoring food and water consumption along with any changes in body weight. Although pain is often associated with weight loss due to anorexia and a decrease in fluid consumption, these measures must be obtained retrospectively and therefore cannot be used to improve the analgesic therapy for that particular animal. However, information can be obtained with respect to specific procedures in that species, which can aid in the treatment of future animals.

Heart rate and respiratory rate have been used as an indirect measure of pain, with increases in both thought to accompany pain states[1]; however such measures should

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[a] Institute of Neuroscience, Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne, Tyne and Wear, NE2 4HH, UK
[b] Comparative Biology Centre, Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne, Tyne and Wear, NE2 4HH, UK
* Corresponding author. Institute of Neuroscience, Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne, Tyne and Wear, NE2 4HH, UK.
E-mail address: claire.richardson@ncl.ac.uk

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be interpreted with caution, as many other factors can influence these parameters. Any stress or excitement, even handing the animal, will increase both heart rate and respiratory rate.[2] Obtaining heart rate and respiratory rates is not only difficult in awake rodents; resting heart rates may be too high to assess by auscultation or palpation of the pulse (eg, >300–400 beats/min).

Clinical Impression of the Animal

In practice the decision to administer an analgesic is often based largely on the veterinarian's clinical impression of an animal. Although not specific, an observation of a change in appearance or behavior in an animal following surgery or in painful conditions often indicates the presence of pain. As the response to pain varies considerably both between species and between individual animals, it is important that pain assessment is performed by clinicians with a comprehensive knowledge of the normal behavior and appearance of the species and animal concerned. These individuals will be the most likely to detect deviations from normal appearance and behavior in the animal. Monitoring at regular intervals is also imperative to ensure continued effective management of pain, particularly in the immediate hours following surgery or injury. Because different assessors may evaluate differently whether an animal is in pain, successive observations by a single observer are likely to provide the best insight into the improvement of an animal over time.

Although the use of pain-scoring scales has not been validated in rodents, it is likely that the use of these systems is preferable to simple observation. Descriptive, numerical, and visual analog (VAS) scales could all be used, but current opinion suggests that VAS may be the most useful in both animals and human infants.[3]

The presence of an observer may also affect the behavior of the animal; for example, many rabbits and guinea pigs often remain immobile.[4] This behavior may be a particular problem when the animal is observed by an unfamiliar person in an unfamiliar environment. It may therefore be beneficial to initially observe such animals from behind a viewing panel or via a video link. A simple web-cam provides an inexpensive means of making these observations.

In summary, while not specific, changes in general appearance and behavior in situations when pain is likely to occur are often indicative of pain. The administration of an analgesic and subsequent prevention or reversal of these behavioral changes can aid in the confirmation of pain. Unfortunately this can be challenging, because analgesics have been shown to influence the behavior of normal animals; for example, administration of buprenorphine leads to increased activity in normal mice.[5] These nonspecific analgesic effects on behavior must be taken into account when assessing the effectiveness of an analgesic.

Behavior-Based Pain-Scoring Systems

Behavior-based pain-scoring systems have been used successfully to study pain in many species. Behaviors such as lip licking, cage circling, and "flank gazing" have been observed in dogs after ovariohysterectomy accompanied by an increase in plasma cortisol, and have been attributed to the presence of pain.[6,7] Similarly, in combination with physiologic measures such as changes in plasma cortisol, specific behavioral responses have been observed in lambs and calves following castration and tail docking.[8,9] Behavior-based pain-scoring systems are now available for many species.[10]

Assessment of Rodents

Rodents do exhibit some signs of pain that are similar to those shown by other animals, including reflex withdrawal responses and vocalizations,[11] yet their specific responses to pain vary. It has been suggested that prey animals such as rats and mice deliberately attempt to disguise behavioral signs of pain to prevent unwanted attention from predators.[12,13] It may also be important for rodents not to show signs of weakness to cage mates to maintain their social status.[14] However, signs of pain in many species are subtle, with the exception of guarding behavior, such as observed with an injured limb. Once key behaviors that are likely to be associated with pain have been identified, it becomes reasonably easy to make an assessment of the intensity of pain being experienced by the animal. However, as mentioned earlier, familiarity with normal behavior is particularly important.

Clinical signs that may indicate pain in rodents are summarized in **Table 1**. In brief, these can include a decrease in general locomotion and a decrease in food and water consumption, with rapid weight loss an important concern. When group-housed, animals in pain may separate themselves from the rest of the group and, depending on cage layout, may remain in a corner or underneath the food hopper. The general appearance of the animal may also change, with it adopting a hunched posture and developing an unkempt coat (both due to piloerection and reduced grooming). When approached, rodents in pain may become unusually aggressive in an attempt to guard the painful area. Abnormal postures may also be more apparent during locomotion because alterations in posture during walking may be used to protect an injured area, for example, back arching[12] in rats and a raised tail position in mice.[15]

Assessment of Rats

In rats, porphyrin staining around the eyes is a nonspecific sign of stress that may indicate a painful state. The presence of porphyrin staining indicates that further pain assessment and a general clinical evaluation should be performed and that the animal should be carefully monitored.

Table 1
Clinical signs that may indicate pain in rodents

Clinical Sign	Description
Abnormal appearance	Lack of grooming Piloerection Hunched posture Porphyrin staining (rats)
Changes to normal behavior	Decrease in normal exploratory behaviors including walking, sniffing, and rearing Increase in other behaviors such as sleeping and time spent stationary Decrease in food and water consumption
Guarding	Alteration in body position or posture to prevent contact with a painful body part
Self mutilation	Excessive grooming, licking, biting, or scratching of the painful area
Vocalization	Particularly when the animal is handled or painful area is palpated Decrease in vocalizations may occur in guinea pigs
Specific behavioral changes	Twitching Abdominal contractions Back arching Belly pressing Walking with tail in a raised position (mice)

Successful behavior-based pain-scoring schemes for use in rats undergoing abdominal surgery have been developed.[12,16] Back arching, twitching, and abdominal contractions have been identified as behaviors that are infrequently observed before surgery, yet the frequency of these behaviors increases following abdominal surgery. Administration of a nonsteroidal anti-inflammatory drug (NSAID) such as carprofen or meloxicam, or an opioid such as buprenorphine decreases the occurrence of these behaviors postsurgically.[16,17]

Assessment of Mice

Following surgical procedures, mice are often fairly active within as little as 1 hour following recovery from anesthesia.[18] This observation has led to the assumption that pain relief may not be necessary, as they appear to behave in a normal manner almost immediately.[19] On closer observation, however, significant changes in behavior can be identified such as twitching, flinching, and writhing along, with a decrease in general exploratory behavior such as walking, rearing, and sniffing.[15,18,20,21]

A new potentially useful method of pain assessment in mice is through analysis of facial expressions. Facial expressions are often used successfully in human infants to assess pain. Recently, the use of facial expressions has been assessed in mice during periods when pain has been induced in laboratory studies.[22] Orbital tightening, nose bulges, cheek bulges, and changes in ear and whisker position have been linked to the presence of pain, and may be useful to indicate when further monitoring of an individual mouse is necessary. It is possible that similar changes may occur in other species.

Assessment of Guinea Pigs and Chinchillas

Limited work has been performed to date on pain assessment in guinea pigs and chinchillas. When handled, normal guinea pigs tend to squeal; however, those assumed to be experiencing pain tend to remain silent. Guinea pigs experiencing acute pain may also show changes in facial expression or aggression toward cage mates. As in other species, chronic pain may result in decreased responsiveness and anorexia.[23]

UNIQUE PHYSIOLOGY

As previously discussed, anorexia frequently occurs in painful conditions; this is particularly a problem in herbivorous rodents such as guinea pigs and chinchillas, which are prone to ileus following periods of anorexia.[24] Dehydration and hypoglycemia may occur in all rodents, so these animals should all be encouraged to eat. For mice and rats, provision of soaked diet on the floor of the cage may be beneficial, and all animals should be presented with a familiar favorite food. Guinea pigs and chinchillas should have good-quality hay readily available, and prokinetics may be administered. If these measures are not sufficiently effective, then syringe feeding may be required.

THERAPEUTICS

Analgesic dose rates based on body weight in rodents tend to be relatively high compared with other mammals, largely because of their small body size and fast metabolic rate. Dose rates of opioid agents given via the oral route are particularly high, due to the considerable first-pass metabolism by the liver (this topic is reviewed for mammalian species elsewhere in this issue).[25]

Systemic Analgesics

The 2 traditional classes of systemic analgesic agents used in rodents are opioids and NSAIDs.

Opioids

In brief, opioid analgesics include: (1) full agonists such as morphine, oxymorphone, hydromorphone, fentanyl, and alfentanil; (2) partial agonists such as buprenorphine; and (3) agonist-antagonists such as butorphanol. Morphine has long been considered to provide the gold standard in pain relief; however, there is sometimes reluctance to use it and the other opioid analgesics because of concerns about potential adverse effects. Although potential adverse effects of opioids such as respiratory depression, nausea,[26] gastrointestinal stasis,[27] and sedation should always be considered, they are often overestimated, and withholding analgesics for fear of adverse effects is not appropriate if animals are carefully monitored. It must be noted that buprenorphine, in common with other opioids, can be associated with pica (the ingestion of inedible substances such as bedding), particularly in rats.[28] If pica is observed, bedding may need to be temporarily removed and animals can be housed on other material to prevent gastric obstruction.

Nonsteroidal anti-inflammatory drugs

NSAIDs act by inhibiting cyclooxygenase (COX) enzymes that are involved in the production of the prostaglandins. Prostaglandins are produced in the first step of the synthesis of prostanoids, which act as mediators in the inflammatory pathway. NSAID activity largely targets the 2 isoforms COX-1 and COX-2.

The NSAID agents most frequently used in rodents include carprofen, meloxicam, and ketoprofen. NSAIDs traditionally have been recommended to alleviate mild pain; however, as the potency and COX selectivity of the newer agents has improved, they can now be used to alleviate more painful conditions. Unlike opioids, NSAIDs are not controlled drugs and may also provide a longer duration of action than many of the opioid agents.

Adverse effects from NSAID administration may target gastrointestinal and renal tissues, therefore NSAID administration is contraindicated in certain conditions such as chronic renal disease. In rodents the most frequently used NSAIDs such as carprofen, ketoprofen, and meloxicam appear to have a wide safety margin.[29–31] Adverse effects are most likely to occur following prolonged NSAID administration, which may be necessary as part of the management of chronic conditions such as arthritis and dental disease. Routine oral administration of low-dose meloxicam for prolonged periods appears to be well tolerated if animals are carefully monitored throughout the course of treatment.

Published analgesic dose rates for rodents tend to be based on either laboratory studies or anecdotal reports, but more reliable data based on postoperative pain assessment is beginning to emerge. Dose rates are summarized in **Table 2**, together with an indication of the quality of evidence supporting the recommendation. There is considerable variation between rodent strains and between individual animals, therefore patients should be carefully assessed (using the criteria outlined in the previous section) before and after analgesic administration.

To facilitate analgesic administration, some analgesic agents (eg, meloxicam) are available as palatable syrups that may be readily accepted by rodents using a small syringe. Analgesics may also be administered in food (eg, buprenorphine jelly)[25] or in drinking water (eg, acetaminophen [paracetamol]). Disadvantages of administration of analgesics via food or drinking water include inadequate dosing when pain results in anorexia and a reduction of drinking. Inadequate dosing will also occur if analgesics are unpalatable. Degradation by hydrolysis over time may also occur with analgesics in drinking water.[32] In addition, most rodents show marked diurnal patterns of water consumption, which would result in prolonged periods during which analgesics would

Table 2
Rodent analgesic dose rates

Drug	Dose (mg/kg)	Route	Interval (hours)	References
A. Rat				
Opioids				
Buprenorphine	0.01–0.05[a]	SC	8–12	17
	0.1–0.25	PO	8–12	10
Butorphanol	1.0–2.0	SC	4	10,19,44
Morphine	2.5	SC	4	10,19,44
Oxymorphone	0.2–0.5	SC		10,44,45
Tramadol	5	SC		10
NSAIDs				
Acetaminophen (paracetamol)	200	PO		10
Carprofen	5.0[a]	SC	12–24	12
	1.0–5.0	PO	12–24	46
Flunixin	2.5	SC		10,44,45
Ketoprofen	5.0[a]	SC		12
Meloxicam	1.0[a]	SC PO	12–24	16
B. Mice				
Opioids				
Buprenorphine	0.05–0.1	SC	12	10,19,44–46
Butorphanol	1.0–2.0	SC	4	10,19,44–46
Morphine	2.5	SC	2–4	10
Oxymorphone	0.2–0.5	SC		10,44
Tramadol	5.0	SC		10
NSAIDs				
Acetaminophen (paracetamol)	200	PO		10
Carprofen	5.0	SC	12–24	10,44,45

Flunixin	2.5	SC		10,44,45
Ketoprofen	5	SC		10
Meloxicam	5[a]	SC, PO	24	10,21
C. Guinea Pigs				
Opioids				
Buprenorphine	0.05	SC	8–12	10,44–46
Butorphanol	1.0–2.0	SC	4	10,44
Morphine	2.0–5.0	SC, IM	4	10,46
Oxymorphone	0.2–0.5	SC		10,44
NSAIDs				
Carprofen	4.0	SC	12–24	10,44
Flunixin	2.5	SC		10,44
Ketoprofen	1.0	SC	12–24	45
Meloxicam	0.1–0.3	SC, PO	24	10,46
D. Chinchillas				
Opioids				
Buprenorphine	0.01–0.05	SC	6–12	44,46
Butorphanol	0.2–2.0	SC	2–4	44–46
NSAIDs				
Carprofen	4.0	SC	24	45
Ketoprofen	1.0	SC	12–24	45,46
Meloxicam	0.1–0.3	SC, PO	24	46

"–" indicates that information is insufficient to make a firm recommendation of an appropriate dose.

Abbreviations: IM, intramuscular; PO, per os (orally); SC, subcutaneous.

[a] Indicates a dose rate based on objective assessment of postoperative pain.

not be consumed. It is therefore recommended that the use of medicated water is always accompanied by other methods of treatment to ensure that analgesia is adequate. When analgesics are administered by injection, the subcutaneous route is generally preferable, as this route is well tolerated by the animal and particularly easy for the operator. The intramuscular route should be avoided or used with caution because of the small muscle mass and, therefore, potential for damage in rodents.

Preventive (or Preemptive) Analgesia

Preventive (formerly termed preemptive) analgesia should be used whenever possible when postsurgical pain is anticipated. Advantages of preventive analgesia include both the reduction of noxious stimuli reaching the central nervous system during surgery and the reduction of peripheral inflammation.[10] The administration of some opioids such as buprenorphine before surgery will have an anesthetic-sparing effect, reducing the dose of anesthetic required during surgery.[33] This effect can easily be incorporated into the anesthetic plan when using inhalant anesthetics; for example, buprenorphine 30 minutes preoperatively allows a reduction of isoflurane maintenance concentrations by about 0.25% to 0.5%.[34] When using injectable anesthetic agents, the effects can be less predictable, so opioid administration before the use of these agents should be performed with caution.[35] Preoperative NSAIDs are usually well tolerated in the well-hydrated patient; however, the potential adverse effects previously discussed may be a concern. Although preventive analgesia is preferable with respect to the efficacy of the agents, drug administration can be challenging and stressful to rodents because of their small size. Analgesics are therefore often combined with anesthetic agents and given as a single injection.[10]

Multimodal Analgesia

Multimodal analgesia refers to the use of different classes of analgesic agents and different sites of administration used to provide more effective analgesia. As nociception involves numerous different mechanisms, the use of multiple analgesics that act in different ways is likely to enhance pain relief. Adverse effects can also be minimized through use of lower doses of each individual drug. An example of a multimodal analgesic regimen for rodents undergoing surgery is to administer buprenorphine preoperatively, infiltrate the surgical field with lidocaine intraoperatively, and administer meloxicam postoperatively.

Local Anesthetics

Local anesthetic agents may be administered: (1) topically (eg, as a cream to facilitate venipuncture),[36] (2) locally by infiltration of the surgical site, (3) in peripheral nerve blocks, or (4) in epidural or spinal anesthesia. Lidocaine and bupivacaine are the most frequently used agents, with bupivacaine having a higher potency and longer duration of action but greater toxicity.

The toxicity of local anesthetics is very similar in large and small mammals; however, the small size of many rodent species makes inadvertent overdose a much more significant hazard. To minimize this risk when using local anesthetics, it is advisable to draw up the maximum safe dose before administration—approximately 10 mg/kg for lidocaine and 2 mg/kg for bupivacaine.[10] Further information on local anesthesia and techniques for performing intratesticular blocks and 5 types of dental blocks are described by Lichtenberger and Ko.[37]

Epidural Analgesia

Opioids may be combined with local anesthetics or administered as single agents via the epidural route. Studies performed in humans suggest that the analgesia produced via the epidural route is likely to be very effective,[38] and although technically challenging this technique is possible in rodents.[39]

Constant-Rate Infusions

Analgesics may be administered to effect when given via constant-rate infusion rather than as a bolus. This route has the advantage of allowing the clinician to minimize the total amount of analgesic used and therefore reduce potential side effects.[37] Constant-rate infusions also avoid “peaks and valleys” in drug concentration and are a valuable component of multimodal analgesia in many veterinary species.[40] Agents that may be used include opioids, ketamine, and α2-adrenoreceptor agonists. Although the use of constant-rate infusions is not frequently reported in companion rodents, this technique is used in the research environment.[41]

Relevance of Studies in Laboratory Animals

Much of what was originally published on the veterinary care of rodents has been based on rodents kept in laboratories. Analgesics available for clinical use have all undergone preclinical testing in laboratory rodents, therefore considerable information about the safety and efficacy of these agents is available and can be referred to when treating pet rodents. This information is valuable in the treatment of companion animal rodent cases. Three factors should remain in consideration when applying findings from laboratory studies: (1) licensing regulations, (2) translation of laboratory studies based on analgesiometry to clinical pain, and (3) differences between pet and laboratory rodent populations.

Licensing

The number of agents approved for domestic rodents is limited despite the copious amount of information on the safety of analgesic agents from laboratory animals. In the United States there are no drugs approved for use in domestic rodents, and only a limited number of licensed products are available within the United Kingdom.[42] Licensing regulations for “off-label use,” permitted in the United States by the Animal Medicinal Drug Use Clarification Act of 1994, should be assessed and discussed with the pet owner prior to administration.

Translation of laboratory studies based on analgesiometric studies to clinical pain

Preclinical testing of analgesic agents on laboratory rodents typically involves assessment of acute pain responses through a variety of analgesiometric tests. Analgesiometric tests typically examine the response to a briefly painful mechanical, thermal, or electrical stimulus, and have been reviewed by Mogil.[43] Although the use of these tests often provides a safe and likely effective dose range for analgesic agents, the dose rates of analgesics that alter responses in analgesiometric tests are not always the most appropriate for treating clinical pain.[10]

Differences between pet and laboratory rodent populations

Laboratory studies are usually performed in young, healthy, adult strains of mice and rats. Dose rate may often need to be adjusted for companion animal rodents, which are often geriatric and may have concurrent diseases. Limited information is available about rodent species such as chinchillas and guinea pigs, which are less frequently used in laboratories.

ADDITIONAL CONCERNS

When considering postoperative pain, environmental factors and supportive care should always be considered. To minimize stress, rodents should be housed away from the sight and smells of their natural predators, including dogs, cats, ferrets, and raptors. Socially housed animals should also ideally be housed with their cage mates. As previously discussed, the use of a viewing panel or video link should be considered for postoperative assessment when monitored by unfamiliar individuals.

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